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Applicant: Whitcomb, J.

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Search Strategy

FILE 'USPATFULL' ENTERED AT 13:46:30 ON 05 DEC 2002

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      E WHITCOMB JEANNETTE/IN
L1      6 S E3 OR E4
L2      20106 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3      7506 S L2 AND (REVERSE TRANSCRIPTASE OR RT)
L4      398 S L3 AND (NNRTI? OR NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBI
L5      2 S L4 AND (CODON 66)
L6      301 S L4 AND (RESISTANCE OR ESCAPE OR MUTANT?)
L7      156 S L6 AND (DRUG-RESISTAN?)
L8      30 S L7 AND (RT/CLM OR REVERSE TRANSCRIPTASE/CLM)
L9      27 S L8 NOT L1
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FILE 'MEDLINE' ENTERED AT 13:57:06 ON 05 DEC 2002

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      E WHITCOMB J/AU
L10     22 S E11-E12
L11     0 S L10 AND (CODON 66 OR 66)
L12     125756 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13     11488 S L12 AND (RESISTANCE OR SUSCEPTIBILITY OR SENSITIVITY)
L14     2276 S L13 AND (REVERSE TRANSCRIPTASE OR RT)
L15     27 S L14 AND (CODON 66 OR 66)
L16     27 S L15 NOT L10
L17     8317 S L12 AND (ANTIRETROVIRAL OR NON-NUCLEOSIDE REVERSE TRANSCRIPTA
L18     2067 S L17 AND (REVERSE TRANSCRIPTASE OR RT OR P66)
L19     0 S L18 AND (CODON 66)
L20     794 S L18 AND (RESIST? OR SUSCEPTIB? OR ESCAPE OR EVASION)
L21     170 S L20 AND (DELAVIRDINE OR NEVIRAPINE OR EFAVIRENZ)
L22     169 S L21 AND (RESIST? OR SUSCEPTIB?)
L23     20 S L21 AND PY=1999
L24     25 S L21 AND PY=2000
L25     23 S L21 AND PY=1998
L26     17 S L21 AND PY=1997
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L1 ANSWER 2 OF 6 USPTAFULL

2002:317266 Means and methods for monitoring nucleoside reverse transcriptase inhibitor antiretroviral therapy and guiding therapeutic decisions in the treatment of HIV/AIDS.

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US 6489098 B1 20021203

APPLICATION: US 1999-339357 19990623 (9)

PRIORITY: US 1998-90547P 19980624 (60)

DOCUMENT TYPE: Utility; GRANTED.

AB This invention relates to antiviral drug susceptibility and resistance tests to be used in identifying effective drug regimens for the treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) and further relates to the means and methods of monitoring the clinical progression of HIV infection and its response to antiretroviral therapy, particularly nucleoside reverse transcriptase inhibitor therapy using phenotypic susceptibility assays or genotypic assays.

CLM What is claimed is:

1. A method of assessing the effectiveness of nucleoside reverse transcriptase antiretroviral therapy of an HIV-infected patient comprising: (a) collecting a plasma sample from the HIV-infected patient; and (b) evaluating whether the plasma sample contains nucleic acid encoding HIV reverse transcriptase having a mutation at codon 69; wherein the mutation results in a substitution of threonine with serine-serine-X, wherein X is an amino acid selected from the group consisting of alanine, glycine, and serine, in which the presence of the mutation at codon 69 correlates with decreased susceptibility to d4T.

2. The method of claim 1, wherein the mutation at codon 69 results in a substitution of threonine with serine-serine-alanine.

3. The method of claim 1, wherein the mutation at codon 69 results in a substitution of threonine with serine-serine-glycine.

4. The method of claim 1, wherein the mutation at codon 69 results in a substitution of threonine with serine-serine-serine.

5. The method of claim 1, wherein the reverse transcriptase has additional mutations, wherein the additional mutations result in (i) a substitution of methionine at codon 41 with leucine; and (ii) a substitution of threonine at codon 215 with tyrosine.

6. The method of claim 1, wherein the HIV-infected patient is being treated with an antiretroviral agent.

7. The method of claim 5, wherein reverse transcriptase has an additional mutation at codon 210, wherein the mutation at codon 210 results in a substitution of leucine with tryptophan.

8. The method of claim 5, wherein reverse transcriptase has an additional mutation at codon 62, wherein the mutation at codon 62 results in a substitution of alanine with valine.

9. The method of claim 8, wherein reverse transcriptase has an additional mutation at codon 210, wherein the mutation at codon 210 results in a substitution of leucine with tryptophan.

10. The method of claim 7, wherein the reverse transcriptase has an additional mutation at codon 75, wherein the mutation at codon 75 results in a substitution of valine with methionine.

11. The method of claim 1, wherein reverse transcriptase has additional mutations at codon 62 and codon 215, wherein the mutation at codon 62 results in a substitution of alanine with valine, and the mutation at codon 215 results in a substitution of threonine with tyrosine or phenylalanine.

12. The method of claim 1, wherein reverse transcriptase has additional mutations at codon 62 and codon 74, wherein the mutation at codon 62 results in a substitution of alanine with valine, and the mutation at codon 74 results in a substitution of leucine with valine.

13. A method of assessing the effectiveness of antiretroviral therapy of an HIV-infected patient comprising: (a) collecting a biological sample from an HIV-infected patient; and (b) evaluating whether the biological sample comprises nucleic acids encoding HIV reverse transcriptase having a mutation at codons 41, 67, 210, 215 and 219, wherein the mutation at codon 41 results in a substitution of methionine with leucine, wherein the mutation at codon 67 results in a substitution of aspartic acid with asparagine, wherein the mutation at codon 210 results in a substitution of leucine with tryptophan, wherein the mutation at codon 215 results in a substitution of threonine with tyrosine, wherein the mutation at codon 219 results in a substitution of lysine with glutamine, and wherein the presence of the mutations correlate with a decrease in d4T susceptibility.

L9 ANSWER 19 OF 27 USPATFULL

2001:82513 Compositions and methods for determining anti-viral drug susceptibility and resistance and anti-viral drug screening.

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US 6242187 B1 20010605

APPLICATION: US 1999-371774 19990810 (9)

PRIORITY: US 1996-10715P 19960129 (60)

DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method for determining susceptibility for an anti-viral drug comprising: (a) introducing a resistance test vector comprising a patient-derived segment and an indicator gene into a host cell; (b) culturing the host cell from (a); (c) measuring expression of the indicator gene in a target host cell; and (d) comparing the expression of the indicator gene from (c) with the expression of the indicator gene measured when steps (a)-(c) are carried out in the absence of the anti-viral drug, wherein a test concentration of the anti-viral drug is present at steps (a)-(c); at steps (b)-(c); or at step (c) This invention also provides a method for determining anti-viral drug resistance in a patient comprising: (a) determining anti-viral drug susceptibility in the patient at a first time using the susceptibility test described above, wherein the patient-derived segment is obtained from the patient at about said time; (b) determining anti-viral drug susceptibility of the same patient at a later time; and (c) comparing the anti-viral drug susceptibilities determined in step (a) and (b), wherein a decrease in anti-viral drug susceptibility at the later time compared to the first time indicates development or progression of anti-viral drug

resistance in the patient. This invention also provides a method for evaluating the biological effectiveness of a candidate anti-viral drug compound. Compositions including resistance test vectors comprising a patient-derived segment and an indicator gene and host cells transformed with the resistance test vectors are provided.

L10 ANSWER 10 OF 22 MEDLINE

1999429225 Document Number: 99429225. PubMed ID: 10501117. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. Little S J; Daar E S; D'Aquila R T; Keiser P H; Connick E; Whitcomb J M; Hellmann N S; Petropoulos C J; Sutton L; Pitt J A; Rosenberg E S; Koup R A; Walker B D; Richman D D. (Department of Medicine, University of California, San Diego, USA.. slittle@ucsd.edu) . JAMA, (1999 Sep 22-29) 282 (12) 1142-9. Journal code: 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB CONTEXT: The transmission of drug-resistant human immunodeficiency virus (HIV) has been documented, but the prevalence of such transmission is unknown. OBJECTIVE: To assess the spectrum and frequency of antiretroviral susceptibility among subjects with primary HIV infection. DESIGN, SETTING, AND PATIENTS: Retrospective analysis of 141 subjects identified from clinical research centers in 5 major metropolitan areas, enrolled from 1989 to 1998, with HIV seroconversion within the preceding 12 months and no more than 7 days' prior antiretroviral (ARV) therapy. MAIN OUTCOME MEASURES: Phenotypic and genotypic ARV susceptibility of HIV from plasma samples. RESULTS: The transmission of drug-resistant HIV as assessed by a greater than 10-fold reduction in ARV susceptibility to 1 or more drugs was observed in 3 (2%) of 141 subjects, including to a nonnucleoside reverse transcriptase inhibitor in 1 patient and to a nucleoside reverse transcriptase inhibitor and a protease inhibitor in 2 patients. Population-based sequence analysis of these 3 samples identified multidrug-resistance mutations in reverse transcriptase (M184V, T215Y, K219K/R) and protease (L101/V, K20R, M36I, M46I, G48V, L63P, A71T, V77I, V82T, 184V, L90M) in the 2 latter patient samples, along with numerous polymorphisms. A reduction in susceptibility of greater than 2.5- to 10-fold to 1 or more drugs was observed in viral isolates from 36 patients (26%). Sequence analysis of these 36 samples identified well-characterized drug resistance mutation in reverse transcriptase and protease in only 1 of these patients. CONCLUSIONS: Reductions in drug susceptibility of more than 10-fold were rare among this cohort of recently HIV-infected subjects and were distributed among each of the 3 major classes of ARV drugs tested. Reductions in susceptibility of more than 2.5- to 10-fold to certain ARV drugs of unknown clinical significance were highly prevalent among newly infected patients. Resistance testing may be warranted to monitor the frequency of drug resistance over time and to assess the potential for geographic variability.

L10 ANSWER 9 OF 22 MEDLINE

2000097805 Document Number: 20097805. PubMed ID: 10634339. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. Havlir D V; Hellmann N S; Petropoulos C J; Whitcomb J M; Collier A C; Hirsch M S; Tebas P; Sommadossi J P; Richman D D. (University of California, San Diego 92103, USA.. dhavlir@ucsd.edu) . JAMA, (2000 Jan 12) 283 (2) 229-34. Journal code: 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB CONTEXT: Loss of viral suppression in patients infected with human immunodeficiency virus (HIV), who are receiving potent antiretroviral therapy, has been attributed to outgrowth of drug-resistant virus; however, resistance patterns are not well characterized in patients whose protease inhibitor combination therapy fails after achieving viral suppression. OBJECTIVE: To characterize drug susceptibility of virus from HIV-infected patients who are failing to sustain suppression while taking an indinavir-containing antiretroviral regimen. DESIGN AND SETTING: Substudy of the AIDS Clinical Trials Group 343, a multicenter clinical research trial conducted between February 1997 and October 1998. PATIENTS:

Twenty-six subjects who experienced rebound (HIV RNA level $>$ or $=$ 200 copies/mL) during indinavir monotherapy (n = 9) or triple-drug therapy (indinavir, lamivudine, and zidovudine; n = 17) after initially achieving suppression while receiving all 3 drugs, and 10 control subjects who had viral suppression while receiving triple-drug therapy. MAIN OUTCOME MEASURE: Drug susceptibility, determined by a phenotypic assay and genotypic evidence of resistance assessed by nucleotide sequencing of protease and reverse transcriptase, compared among the 3 patient groups. RESULTS: Indinavir resistance was not detected in the 9 subjects with viral rebound during indinavir monotherapy or in the 17 subjects with rebound during triple-drug therapy, despite plasma HIV RNA levels ranging from 10(2) to 10(5) copies/mL. In contrast, lamivudine resistance was detected by phenotypic assay in rebound isolates from 14 of 17 subjects receiving triple-drug therapy, and genotypic analyses showed changes at codon 184 of reverse transcriptase in these 14 isolates. Mean random plasma indinavir concentrations in the 2 groups with rebound were similar to those of a control group with sustained viral suppression, although levels below 50 ng/mL were more frequent in the triple-drug group than in the control group (P = .03). CONCLUSIONS: Loss of viral suppression may be due to suboptimal antiviral potency, and selection of a predominantly indinavir-resistant virus population may be delayed for months even in the presence of ongoing indinavir therapy. The results suggest possible value in assessing strategies using drug components of failing regimens evaluated with resistance testing.

L10 ANSWER 8 OF 22 MEDLINE

2000187151 Document Number: 20187151. PubMed ID: 10722492. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. Petropoulos C J; Parkin N T; Limoli K L; Lie Y S; Wrin T; Huang W; Tian H; Smith D; Winslow G A; Capon D J; Whitcomb J M. (ViroLogic, Inc., South San Francisco, California 94080, USA.. cpetropoulos@virologic.com) . ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (2000 Apr) 44 (4) 920-8. Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Although combination antiretroviral therapy has resulted in a considerable improvement in the treatment of human immunodeficiency virus (HIV) type 1 (HIV-1) infection, the emergence of resistant virus is a significant obstacle to the effective management of HIV infection and AIDS. We have developed a novel phenotypic drug susceptibility assay that may be useful in guiding therapy and improving long-term suppression of HIV replication. Susceptibility to protease (PR) and reverse transcriptase (RT) inhibitors is measured by using resistance test vectors (RTVs) that contain a luciferase indicator gene and PR and RT sequences derived from HIV-1 in patient plasma. Cells are transfected with RTV DNA, resulting in the production of virus particles that are used to infect target cells. Since RTVs are replication defective, luciferase activity is measured following a single round of replication. The assay has been automated to increase throughput and is completed in 8 to 10 days. Test results may be useful in facilitating the selection of optimal treatment regimens for patients who have failed prior therapy or drug-naïve patients infected with drug-resistant virus. In addition, the assay can be used to evaluate candidate drugs and assist in the development of new drugs that are active against resistant strains of HIV-1.

L10 ANSWER 7 OF 22 MEDLINE

2001031501 Document Number: 20499048. PubMed ID: 11044070. Reduced susceptibility of human immunodeficiency virus type 1 (HIV-1) from patients with primary HIV infection to nonnucleoside reverse transcriptase inhibitors is associated with variation at novel amino acid sites. Brown A J; Precious H M; Whitcomb J M; Wong J K; Quigg M; Huang W; Daar

E S; D'Aquila R T; Keiser P H; Connick E; Hellmann N S; Petropoulos C J; Richman D D; Little S J. (Centre for HIV Research, Institute of Cell, Animal and Population Biology, University of Edinburgh, Edinburgh, Scotland.. A.Leigh-Brown@ed.ac.uk) . JOURNAL OF VIROLOGY, (2000 Nov) 74 (22) 10269-73. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Recently, significant numbers of individuals with primary human immunodeficiency virus (HIV) infection have been found to harbor viral strains with reduced susceptibility to antiretroviral drugs. In one study, HIV from 16% of such antiretroviral-naive individuals was shown to have a susceptibility to nonnucleoside reverse transcriptase (RT) inhibitors (NNRTIs) between 2.5- and 10-fold lower than that of a wild-type control. Mutations in the RT domain that had previously been associated with antiretroviral resistance were not shared by these strains. We have analyzed by logistic regression 46 variable amino acid sites in RT for their effect on susceptibility and have identified two novel sites influencing susceptibility to NNRTIs: amino acids 135 and 283 in RT. Eight different combinations of amino acids at these sites were observed among these patients. These combinations showed a 14-fold range in mean susceptibility to both nevirapine and delavirdine. In vitro mutagenesis of the control strain combined with a phenotypic assay confirmed the significance of amino acid variation at these sites for susceptibility to NNRTIs.

L10 ANSWER 3 OF 22 MEDLINE

2002613194 Document Number: 22257107. PubMed ID: 12370521.

Hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in HIV-1: clinical, phenotypic and genotypic correlates. Whitcomb Jeannette M; Huang Wei; Limoli Kay; Paxinos Ellen; Wrin Terri; Skowron Gail; Deeks Steven G; Bates Michael; Hellmann Nicholas S; Petropoulos Christos J. (ViroLogic Inc., South San Francisco, University of California at San Francisco and San Francisco General Hospital, San Francisco, California and the Roger Williams Medical Center/Brown University, Providence, Rhode Island, USA.) AIDS, (2002 Oct 18) 16 (15) F41-7. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB OBJECTIVE The routine use of phenotypic drug resistance testing in patient management has revealed that many HIV-1 strains possess significantly increased drug sensitivity, or 'hypersusceptibility' compared with wild-type viruses. This study describes hypersusceptibility to non-nucleoside reverse transcriptase inhibitors (NNRTI) and was designed to determine the prevalence of and viral characteristics associated with NNRTI hypersusceptibility in patient-derived viruses. METHODS Retrospective analyses were performed on a large clinical laboratory dataset containing phenotypic drug susceptibility and genotypic sequence results from HIV-1 patient isolates. Genetically engineered viruses were used to confirm the role of certain nucleoside reverse transcriptase inhibitor (NRTI)-resistance mutations in NNRTI hypersusceptibility. RESULTS Hypersusceptibility to delavirdine, efavirenz and nevirapine was detected in 10.7, 10.8 and 8.0% of more than 17 000 consecutive plasma samples submitted for phenotypic susceptibility testing. In analyses limited to a subset of viruses derived from patients with known treatment histories, NNRTI hypersusceptibility was observed significantly more frequently among viruses from NRTI experienced/NNRTI-naive patients compared with viruses from NRTI/NNRTI-naive patients. Significant inverse correlations between NRTI and NNRTI susceptibility exist among the viruses from NRTI-experienced patients. Analyses of viruses classified according to their NNRTI susceptibility identified 18 positions in reverse transcriptase where substitutions were significantly associated with NNRTI

hypersusceptibility. CONCLUSIONS NNRTI hypersusceptibility is common among patient HIV-1 isolates, especially in NRTI-resistant viruses. Genotypic correlates of hypersusceptibility are complex and not easily defined by a simple analysis of NRTI-associated resistance mutations. NNRTI hypersusceptibility may provide an explanation for the superior virologic response to NNRTI-containing salvage regimens observed in NRTI-experienced patients in several clinical trials.

L10 ANSWER 2 OF 22 MEDLINE

2002633210 Document Number: 22257106. PubMed ID: 12370520. The clinical relevance of non-nucleoside reverse transcriptase inhibitor hypersusceptibility: a prospective cohort analysis. Haubrich Richard H; Kemper Carol A; Hellmann Nicholas S; Keiser Philip H; Witt Mallory D; Forthal Donald N; Leedom John; Leibowitz Matthew; Whitcomb Jeannette M; Richman Douglas; McCutchan J Allen. (University of California at San Diego, San Diego, California, USA. (California Collaborative Treatment Group).) AIDS, (2002 Oct 18) 16 (15) F33-40. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB OBJECTIVE: To evaluate the clinical significance of hypersusceptibility to non-nucleoside reverse transcriptase inhibitors (NNRTI). DESIGN: Analysis of a prospective clinical trial cohort. PATIENTS: NNRTI-naïve patients failing a stable antiretroviral regimen. MEASUREMENTS: HIV phenotype, HIV RNA, and CD4 cell counts were prospectively collected after patients changed to a new regimen. Hypersusceptibility to NNRTI was defined as a fold-change (FC) in IC50 (inhibitory concentration of 50%) of < 0.4. RESULTS: The 177 patients had a mean HIV RNA of 4.1 log10 copies/ml, CD4 cell count of 322 x 10(6) cells/l and 41 months of prior antiretroviral treatment. Hypersusceptibility to one or more NNRTI was present in 29%. Both longer duration and reduced susceptibility to nucleoside reverse transcriptase inhibitors were associated with efavirenz hypersusceptibility (P < 0.05). NNRTI-containing regimens were initiated in 106 patients at baseline. The mean change in log HIV RNA after 6 months was greater for patients with hypersusceptibility (-1.2 log10 copies/ml; n = 21) than in patients without (-0.8 log10 copies/ml; n = 77) (P = 0.016). Differences persisted to month 12 (P = 0.023). Multiple linear regression models confirmed that hypersusceptibility to NNRTI was a significant independent predictor of the magnitude of early (months 1-4) HIV RNA reduction, after accounting for the baseline HIV RNA and the number of drugs to which the patient's virus was susceptible (P < 0.02). CD4 cell increases (months 4-10) were 28- 60 x 10(6) cells/l greater in patients with hypersusceptible virus (P < or = 0.1). CONCLUSION: NNRTI hypersusceptibility occurred in more than 20% of nucleoside-experienced patients and was associated with greater reduction of HIV RNA and increase in CD4 cells.

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L24 ANSWER 25 OF 25 MEDLINE

2000134609 Document Number: 20134609. PubMed ID: 10669367. Antiretroviral resistance mutations in human immunodeficiency virus type 1 reverse transcriptase and protease from paired cerebrospinal fluid and plasma samples. Venturi G; Catucci M; Romano L; Corsi P; Leoncini F; Valensin P E; Zazzi M. (Sezione di Microbiologia, Dipartimento di Biologia Molecolare, Universita di Siena, Italy.) JOURNAL OF INFECTIOUS DISEASES, (2000 Feb) 181 (2) 740-5. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Twenty-four adults infected with human immunodeficiency virus type 1 (HIV-1) with central nervous system symptoms were studied for antiretroviral resistance

mutations in HIV-1 RNA obtained from paired cerebrospinal fluid (CSF) and plasma samples. Paired sequences were obtained from 21 and 13 patients for reverse transcriptase (RT) and for protease, respectively. Mutations conferring resistance to the RT inhibitors zidovudine, lamivudine, or nevirapine were detected in 14 patients, including 11 pretreated and 3 drug-naive subjects. The mutation patterns in the 2 compartments were different in most patients. Genotypic resistance to protease inhibitors was detected in both plasma and CSF from 1 patient treated with multiple protease inhibitors. However, accessory protease inhibitor resistance mutations at polymorphic sites were different in plasma and CSF in several patients. Partially independent evolution of viral quasispecies occurs in plasma and CSF, raising the possibility that compartmentalization of drug resistance may affect response to antiretroviral treatment.

L24 ANSWER 24 OF 25 MEDLINE
2000170570 Document Number: 20170570. PubMed ID: 10708276. Non-nucleoside reverse transcriptase inhibitor resistance among patients failing a nevirapine plus protease inhibitor-containing regimen. Casado J L; Hertogs K; Ruiz L; Dronda F; Van Cauwenberge A; Arno A; Garcia-Arata I; Bloor S; Bonjoch A; Blazquez J; Clotet B; Larder B. (Infectious Diseases Unit, Ramon y Cajal Hospital, Madrid, Spain.. jcasado@hrc.insalud.es) . AIDS, (2000 Jan 28) 14 (2) F1-7. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To determine the rate of nevirapine resistance in patients failing a nevirapine plus protease inhibitor (PI)-based regimen, and whether these isolates remain susceptible to other non-nucleoside reverse transcriptase inhibitors (NNRTI).
DESIGN AND SETTING: A retrospective cohort study in two tertiary university hospitals. PATIENTS: Eighty-eight HIV-infected, NNRTI-naive patients receiving nevirapine plus PI as a rescue regimen after PI treatment failure. MAIN OUTCOME MEASURES: Genotypic and phenotypic resistance data at inclusion (73 and 60 plasma samples, respectively) and after 24 weeks (53 and 42 samples). RESULTS: Baseline phenotypic susceptibility to nevirapine was found in 70% of patients, and similar data were observed for efavirenz (91%) and delavirdine (71%). NNRTI resistance-associated mutations were found in 11 patients (12.5%). At 24 weeks, resistant isolates to nevirapine were found in 92% of patients, and correlated with similar resistance to efavirenz (68%) and delavirdine (73%). In the genotypic analysis, the Y181 C mutation was observed in 76% of mutants, and the most common changes were a combination of mutations at positions Y181C/K103N (23%) and the single mutation Y181C (15%). The development of nevirapine resistance was associated with baseline resistance to PI included in the regimen ($P=0.01$). For isolates containing the single amino acid substitution Y181C, 29% remained fully susceptible to efavirenz, whereas 14% showed intermediate resistance to efavirenz and delavirdine. CONCLUSION: The failure of a nevirapine plus PI-containing regimen is associated with nevirapine resistance in most patients, with the most common mutation occurring at amino acid residue 181. Although there is a high degree of cross-resistance among NNRTI, nearly one third of resistant isolates carrying the single Y181C mutation remain susceptible to efavirenz.

L24 ANSWER 21 OF 25 MEDLINE

2000187680 Document Number: 20187680. PubMed ID: 10720543.

Resistance profiles in patients with viral rebound on potent antiretroviral therapy. Cozzi Lepri A; Sabin C A; Staszewski S; Hertogs K; Muller A; Rabenau H; Phillips A N; Miller V. (Royal Free Centre for HIV Medicine and Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London, United Kingdom.) JOURNAL OF INFECTIOUS DISEASES, (2000 Mar) 181 (3) 1143-7. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB The prevalence of phenotypic drug resistance was assessed in 60 patients with a viral rebound after they received a protease inhibitor (PI)- or nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen (baseline). Resistance testing was done within 36 weeks of viral rebound; no resistance testing was available at baseline. All patients had previously received zidovudine; 86.0% had received lamivudine. In total, 45.1% of the patients had strains resistant to the PI that they started and 88.9% given nevirapine had strains with reduced susceptibility to that drug. Overall, 46 patients (76.7%) harbored a strain resistant to ≥ 1 drug of their initial PI- or NNRTI-containing regimen. Of 53 patients who remained on treatment at the time of the study (40 had switched to a different combination from that at baseline), 6 harbored isolates susceptible to all drugs they had ever received. Thus, patients with viral rebound while on potent antiretroviral therapy usually have reduced susceptibility to ≥ 1 drug. Viral rebound also occurs in persons in whom resistant strains could not be detected by the assay used.

L24 ANSWER 20 OF 25 MEDLINE

2000242011 Document Number: 20242011. PubMed ID: 10779379. Mutational analysis of trp-229 of human immunodeficiency virus type 1 reverse transcriptase (RT) identifies this amino acid residue as a prime target for the rational design of new non-nucleoside RT inhibitors. Pelemans H; Esnouf R; De Clercq E; Balzarini J. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium.) MOLECULAR PHARMACOLOGY, (2000 May) 57 (5) 954-60. Journal code: 0035623. ISSN: 0026-895X. Pub. country: United States. Language: English.

AB Trp-229 is part of the non-nucleoside reverse transcriptase inhibitor (NNRTI)-binding pocket of HIV type 1 (HIV-1) reverse transcriptase (RT), and is also part of the "primer grip" of HIV-1 RT. Using site-directed mutagenesis, seven RT mutants were constructed bearing the mutations 229Phe, 229Tyr, 229Ile, 229His, 229Lys, 229Cys, and 229Gln. We found that all of the mutants showed severely compromised RNA- and DNA-dependent DNA polymerase activities ($< 2\%$ of wild-type activity). The recombinant 229Phe and 229Tyr RT enzymes were among the mutant enzymes with the highest activity (0.7 and 1.1% of wild-type activity, respectively) and we evaluated these for resistance against several NNRTIs. No resistance was found for the 229Phe RT, but the 229Tyr RT showed a approximately 20-fold resistance against UC-781 and lower resistance against emivirine and nevirapine. Attempts to make recombinant virus strains bearing the single 229Phe or 229Tyr RT mutation failed. Experiments in which we varied the pentaenyl ether substituent of the thiocarboxanilide UC-781 revealed that Trp-229 can be specifically targeted by NNRTIs and that an alkenyloxy group length of five atoms assures an optimal interaction of

the thiocarboxanilides with Trp-229. Our findings indicate that Trp-229, when combined with other crucial immutable amino acids (i.e., Tyr-318), is an appropriate candidate for the targeted design of new NNRTIs.

L24 ANSWER 15 OF 25 MEDLINE
2000411061 Document Number: 20351799. PubMed ID: 10891870. Clinical uses of non-nucleoside reverse transcriptase inhibitors. Harris M; Montaner J S. (AIDS Research Program, St. Paul's Hospital, Vancouver, B.C., Canada.) REVIEWS IN MEDICAL VIROLOGY, (2000 Jul-Aug) 10 (4) 217-29. Ref: 60. Journal code: 9112448. ISSN: 1052-9276. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Three non-nucleoside reverse transcriptase inhibitors (NNRTIs) are currently available for treatment of HIV-1 as part of combination antiretroviral therapy. Oral dosing is administered three times daily for delavirdine (DLV), twice daily for nevirapine (NVP), and once daily for efavirenz (EFV). Rash is a common side effect of all three NNRTIs, and early CNS side effects are also frequent with EFV. Hepatotoxicity is relatively uncommon but requires appropriate monitoring. Drug interactions mediated by the cytochrome P450 system are an important consideration when the NNRTIs are administered concomitantly with other drugs, including protease inhibitors (PIs). HIV strains with reduced susceptibility to NNRTIs can occur with a single mutation in the reverse transcriptase (RT) gene. The available NNRTIs exhibit overlapping genotypic resistance patterns, but newer agents may overcome this problem. NNRTIs have been studied in combination with nucleoside RT inhibitors for first-line HIV therapy, where they have shown at least equivalent antiviral efficacy compared with PI-based regimens over 1-2 years of therapy. NVP and EFV have also been studied as a replacement for a PI within a virologically successful regimen, with the aim of preventing or reducing PI toxicities and simplifying the dosing regimen. Such 'switch' strategies are successful for certain patients in maintaining virologic suppression for 6 months or more and result in varying degrees of improvement in PI-associated toxicities. NNRTIs may offer a benefit when included in salvage regimens for patients failing PI-based therapy, particularly in patients who have not previously been treated with NNRTIs. NVP has been shown to have a substantial favourable impact on the rate of vertical HIV-1 transmission with a simple, cost-effective regimen.
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L24 ANSWER 11 OF 25 MEDLINE
2000485091 Document Number: 20382587. PubMed ID: 10922953. [Non-nucleoside reverse transcriptase inhibitors]. Inhibiteurs non nucleosidiques de la transcriptase inverse. Joly V; Yeni P. (Service de Medecine Interne, Hopital Bichat, 75877 Paris Cedex 18.) ANNALES DE MEDECINE INTERNE, (2000 Jun) 151 (4) 260-7. Ref: 64. Journal code: 0171744. ISSN: 0003-410X. Pub. country: France. Language: French.

AB The non-nucleoside reverse transcriptase inhibitors (NNRTIs) directly inhibit the HIV-1 reverse transcriptase (RT) by binding in a reversible and non-competitive manner to the enzyme. The currently available NNRTIs are nevirapine, delavirdine, and efavirenz; other compounds are under evaluation. NNRTIs are extensively metabolized in the liver through cytochrome P450, leading to pharmacokinetic interactions with compounds utilizing the same

metabolic pathway, particularly PIs, whose plasma levels are altered in the presence of NNRTIs. NNRTIs are drugs with a low genetic barrier, i.e. a single mutation in RT genome induces a high-level of phenotypic resistance, preventing the use of NNRTIs as monotherapy. In naive patients, several trials have shown the value of NNRTIs in combination with nucleosides and/or protease inhibitors. Small pilot studies have shown that NNRTIs may be useful as second-line therapy. However, due to the rapid emergence of resistant virus to these compounds in case of incomplete viral suppression, NNRTIs should not be added to current failing antiretroviral regimen. The most common side-effect reported with nevirapine and delavirdine is rash. The incidence of rash is rather similar under these two compounds, but severe rash is less frequent with delavirdine. The most common adverse reactions reported with efavirenz are central nervous system complaints such as dizziness. Rash is reported less frequently than with nevirapine or delavirdine, and is usually mild. NNRTIs resistance mutations are located in the amino acid residues aligning the NNRTI-binding "pocket" site. High-level resistance is often associated with a single point mutation which develops within this site (especially codon groups 100 - 108 and 181 - 190). Patients failing on one NNRTI are very likely to possess multiple NNRTI resistance mutations. NNRTIs should always be used as part of a potent antiretroviral therapy to insure suppression of viral replication, thus circumventing the rapid selection of cross-resistant variants.

L23 ANSWER 17 OF 20 MEDLINE
1999254330 Document Number: 99254330. PubMed ID: 10321027. Perspectives
of non-nucleoside reverse
transcriptase inhibitors (NNRTIs) in the therapy of
HIV-1 infection. De Clercq E. (Rega Institute for Medical
Research, Katholieke Universiteit Leuven, Belgium.) FARMACO, (1999
Jan-Feb) 54 (1-2) 26-45. Ref: 157. Journal code: 8912641. ISSN:
0014-827X. Pub. country: Italy. Language: English.

AB Non-nucleoside reverse transcriptase
inhibitors (NNRTIs) have, in addition to the nucleoside
reverse transcriptase inhibitors (NRTIs) and protease
inhibitors (PIs), gained a definitive place in the treatment of
HIV-1 infections. Starting from the HEPT and TIBO derivatives,
more than thirty structurally different classes of compounds have been
identified as NNRTIs, that is compounds that are specifically inhibitory
to HIV-1 replication and targeted at the HIV-1
reverse transcriptase (RT). Two NNRTIs (nevirapine and delavirdine) have been formally licensed
for clinical use and several others are (or have been) in preclinical
and/or clinical development [tetravirapine (TIBO R-86183), loviride
(alpha-APA R89439), thiocarboxanilide UC-781, HEPT derivative MKC-442,
quinoxaline HBY 097, DMP 266 (efavirenz), PETT derivatives
(troviridine, PETT-4, PETT-5) and the dichlorophenylthio(pyridyl)imidazole
derivative S-1153]. The NNRTIs interact with a specific 'pocket' site of
HIV-1 RT that is closely associated with, but distinct
from, the NRTI binding site. NNRTIs are notorious for rapidly eliciting
resistance due to mutations of the amino acids surrounding the
NNRTI-binding site. However, the emergence of resistant
HIV strains can be circumvented if the NNRTIs, preferably in
combination with other anti-HIV agents, are used from the start
at sufficiently high concentrations. In vitro, this procedure has been
shown to 'knock-out' virus replication and to prevent resistance
from arising. In vivo, various triple-drug combinations containing NNRTIs,
NRTIs and/or PIs may result in an effective viral suppression and ensuing

immune recovery. However, this so-called HAART (highly active antiretroviral therapy) may also fail, and this necessitates the design of new and more effective drugs and drug cocktails.

L23 ANSWER 7 OF 20 MEDLINE

2000051622 Document Number: 20051622. PubMed ID: 10584233.

Antiretroviral agent nevirapine: its pharmacological action and potential for clinical use. Takeuchi S; Osugi T. (Department of Pharmacology, Kawanishi Pharma Research Institute, Nippon Boehringer Ingelheim Co., Ltd., Japan.) NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (1999 Oct) 114 (4) 205-11. Ref: 26. Journal code: 0420550. ISSN: 0015-5691. Pub. country: Japan. Language: Japanese.

AB Nevirapine (NVP) is a potent noncompetitive inhibitor of the reverse transcriptase enzyme, which is necessary for HIV replication. NVP selectively inhibits HIV-1 but not HIV-2 and any of the human DNA polymerases. NVP is active against ZDV-resistant HIV-1 and synergistic with nonnucleoside reverse transcriptase inhibitors. NVP has a favorable pharmacokinetic profile, becomes widely distributed throughout body tissues including the central nervous system, and is active in the adult at an oral dose of 200 mg administered twice daily after a 2 week lead-in dose of 200 mg/day due to its long elimination half life. Although the currently used protease inhibitors (PIs) may undergo more rapid rates of metabolism because NVP induces CYP3A, No dosage adjustments are required when NVP is taken in combination with PIs so far. When administered in triple combinations with antiretroviral agents, the antiviral effect of NVP has been profound and sustained in HIV-infected patients, particularly in naive patients to antiretroviral therapy. Resistance to NVP is rapid when given as monotherapy, but this is altered and made less clinically relevant when NVP is administered as a triple combination. NVP has a safety profile that does not overlap with other antiretroviral therapies, the most common treatment-limiting reaction being rash. It seems that NVP would be a very useful option in combination with antiretroviral agents.

L25 ANSWER 10 OF 23 MEDLINE

2001282415 Document Number: 99704248. PubMed ID: 11365807. NNRTIs: a neglected class. Cadman J. GMHC TREATMENT ISSUES, (1998 Sep) 12 (9) 6-10. Journal code: 9509489. ISSN: 1077-1824. Pub. country: United States. Language: English.

AB Non-nucleoside reverse transcriptase inhibitors (NNRTI) are a class of antiretrovirals that are effective in suppressing viral activity when used in combination with other antiretroviral agents. Nevirapine, Delavirdine, and efavirenz are all NNRTIs approved by the Food and Drug Administration. Researchers found that there is high cross resistance within NNRTIs, but cross resistance to drugs in other classes remains small. Studies indicate that treatment with protease inhibitors is possible after treatment failure with NNRTIs. Nevirapine was shown to be most effective in trials with triple combination regimens. Other studies looking at the effectiveness of Nevirapine are discussed. Delavirdine, taken three times a day, showed favorable results in triple combination therapy, and is considered a good option for primary therapy. Trials employing different levels of Delavirdine and protease inhibitors are reviewed, as is the use of Delavirdine and other NNRTIs in salvage therapy.

L25 ANSWER 16 OF 23 MEDLINE

1999095043 Document Number: 99095043. PubMed ID: 9878993.
Efavirenz. Adkins J C; Noble S. (Adis International Limited,
Auckland, New Zealand.. demail@adis.co.nz) . DRUGS, (1998 Dec)
56 (6) 1055-64; discussion 1065-6. Ref: 34. Journal code: 7600076. ISSN:
0012-6667. Pub. country: New Zealand. Language: English.

AB Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which shows good inhibitory activity against HIV-1. Reduced susceptibility to efavirenz has been reported with HIV-1 variants containing single and multiple mutations to the reverse transcriptase enzyme. In vitro and in vivo data suggest that the resistance profile of efavirenz overlaps with that of the NNRTIs nevirapine and delavirdine. Clinically significant drug interactions have been reported with efavirenz and indinavir and saquinavir. An increase in dosage of indinavir from 800 to 1000 mg 3 times daily is recommended during coadministration with efavirenz. Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended. Once-daily efavirenz in combination with zidovudine plus lamivudine or indinavir or nelfinavir increased CD4+ cell counts and reduced HIV RNA plasma levels to below quantifiable levels (< 400 copies/ml) in HIV-infected patients. A sustained reduction in viral load was maintained for at least 72 weeks in 1 study. Nervous system symptoms (including headache, dizziness, insomnia and fatigue) and dermatological effects (including maculopapular rash) appear to be the most common adverse events reported with efavirenz-containing antiretroviral regimens.

L25 ANSWER 19 OF 23 MEDLINE
1998425881 Document Number: 98425881. PubMed ID: 9754886. The role of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 infection. De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.) ANTIVIRAL RESEARCH, (1998 Jun) 38 (3) 153-79. Ref: 137. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have, in addition to the nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs), gained a definitive place in the treatment of HIV-1 infections. Starting from the HEPT and TIBO derivatives, more than 30 structurally different classes of compounds have been identified as NNRTIs, that is compounds that are specifically inhibitory to HIV-1 replication and targeted at the HIV-1 reverse transcriptase (RT). Two NNRTIs (nevirapine and delavirdine) have been formally licensed for clinical use and several others are in preclinical or clinical development [thiocarboxanilide UC-781, HEPT derivative MKC-442, quinoxaline HBY 097 and DMP 266 (efavirenz)]. The NNRTIs interact with a specific 'pocket' site of HIV-1 RT that is closely associated with, but distinct from, the NRTI binding site. NNRTIs are notorious for rapidly eliciting resistance due to mutations of the amino acids surrounding the NNRTI-binding site. However, the emergence of resistant HIV strains can be circumvented if the NNRTIs, alone or in combination, are used from the start at sufficiently high concentrations. In vitro, this procedure has proved to 'knock-out' virus replication and to prevent resistance from arising. In vivo, various triple-drug combinations of NNRTIs (nevirapine, delavirdine or efavirenz) with

NRTIs (AZT, 3TC, ddI or d4T) and/or PIs (indinavir or nelfinavir) have been shown to afford a durable anti-HIV activity, as reflected by both a decrease in plasma HIV-1 RNA levels and increased CD4 T-lymphocyte counts.

L26 ANSWER 12 OF 17 MEDLINE
1998122269 Document Number: 98122269. PubMed ID: 9462437. In-vitro selection of HIV-1 variants resistant to non-nucleoside reverse transcriptase inhibitors in monocyte-derived macrophages. Been-Tiktak A M; de Haas C J; de Graaf L; Boucher C A; Verhoef J; Borleffs J C; Nottet H S; Schuurman R. (Eijkman-Winkler Institute of Medical Microbiology, University of Utrecht, University Hospital, The Netherlands.) JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, (1997 Dec) 40 (6) 847-53. Journal code: 7513617. ISSN: 0305-7453. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Unlike the selection of HIV-1 variants resistant to anti-retroviral drugs in human peripheral blood mononuclear cells and T cell lines, induction of resistance in monocyte-derived macrophages has not been widely studied. Since macrophages serve as a potential HIV-1 reservoir in humans, knowledge of the effect of anti-retroviral drugs on macrophage-tropic HIV-1 isolates may help in the design of a strategy for prolonged suppression of viral replication. In-vitro selection and drug susceptibility testing of macrophage-tropic HIV-1 variants with reduced sensitivity to two non-nucleoside reverse transcriptase inhibitors, atevirdine and delavirdine (both bis-heteroarylpiperazines), is described here. The atevirdine-resistant isolate was cross-resistant to delavirdine, and the delavirdine-resistant isolate was cross-resistant to atevirdine. Interestingly, the atevirdine-resistant isolate, but not the delavirdine-resistant isolate, was also cross-resistant to nevirapin while the inhibition of viral replication of both isolates in macrophages by zidovudine was the same as that in the parental HIV-1 strain. Nucleotide sequence analysis of the resistant macrophage-tropic HIV-1 isolates showed that the atevirdine-induced resistance was due to a single amino acid change at codon 106 and that the delavirdine-induced resistance could be attributed to an amino acid change at codon 236. This study demonstrates that monocyte-derived macrophages can be used to investigate the phenotypic and genotypic acquisition of anti-retroviral drug resistance of macrophage-tropic HIV-1.

L26 ANSWER 14 OF 17 MEDLINE
97323998 Document Number: 97323998. PubMed ID: 9180194. Transmission of human immunodeficiency virus type 1 resistant to nevirapine and zidovudine. Sydney Primary HIV Infection Study Group. Imrie A; Beveridge A; Genn W; Vizzard J; Cooper D A. (Centre for Immunology, St Vincent's Hospital, Grosvenor Clinic, Woolhara, Australia.) JOURNAL OF INFECTIOUS DISEASES, (1997 Jun) 175 (6) 1502-6. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Human immunodeficiency virus type 1 (HIV-1) resistant to the nonnucleoside reverse transcriptase inhibitor nevirapine and to the nucleoside analogue zidovudine was transmitted from a homosexual man to his sex partner. The virus source patient had commenced combination zidovudine and nevirapine therapy 2.5 years prior to his partner's primary

HIV infection. He received both therapies for 7 months, then discontinued nevirapine treatment, continuing to receive zidovudine monotherapy for a further 16 months. He had ceased zidovudine therapy 6 months before the time of his partner's seroconversion. Analysis of major and minor isolates obtained from both patients soon after onset of the recipient's primary HIV infection illness confirmed that an HIV-1 variant mutant at codons 70, 98, and 181 of the viral reverse transcriptase was transmitted. This is the first documented case of transmission of HIV-1 resistant to two antiretroviral compounds.

L26 ANSWER 17 OF 17 MEDLINE
97240701 Document Number: 97240701. PubMed ID: 9086161. High-dose nevirapine in previously untreated human immunodeficiency virus type 1-infected persons does not result in sustained suppression of viral replication. de Jong M D; Vella S; Carr A; Boucher C A; Imrie A; French M; Hoy J; Sorice S; Pauluzzi S; Chiodo F; Weverling G J; van der Ende M E; Frissen P J; Weigel H M; Kauffmann R H; Lange J M; Yoon R; Moroni M; Hoenderdos E; Leitz G; Cooper D A; Hall D; Reiss P. (National AIDS Therapy Evaluation Centre, Department of Infectious Diseases, University of Amsterdam, Netherlands.) JOURNAL OF INFECTIOUS DISEASES, (1997 Apr) 175 (4) 966-70. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB High-dose nevirapine treatment has been reported to confer sustained antiretroviral effects, despite a rapid development of resistance. The use of this strategy was evaluated in 20 previously untreated human immunodeficiency virus type 1 (HIV-1) p24 antigenemic persons with CD4 cell counts between 100 and 500/mm³. Treatment consisted of 400 mg of nevirapine, after a 2-week lead-in dose of 200 mg. Rash was the most frequently reported adverse event, occurring in 25%. While sustained declines in p24 antigen levels were observed in the majority, serum HIV-1 RNA load and CD4 cell counts returned to baseline values within 12 weeks in virtually all subjects. The resistance -conferring tyrosine-to-cysteine substitution at reverse transcriptase position 181 was detected after 4 weeks in most subjects. These observations suggest that plasma drug levels attained with high-dose nevirapine were not sufficient to inhibit nevirapine-resistant virus, although they were approximately 2-fold higher than reported IC₅₀ values of resistant virus.